II. REMARKS

Upon entry of the present amendment, claims 63, 66-71, 74, 75, 78-81, 84-90, 93, 94, 97-102, and 105-145 will be pending in the present application. Claims 63, 71, 75, 81, 88, 90, 94, 101, 102, 107, 111, 113, 115-121, and 133-138 are amended herein. No new matter is added with the amendments or newly added claims. The amendments to claims 88, 101, 107, 111, 113, 115-121, and 133-138 are corrections to minor formatting or typographical errors. Newly added claims 139-145 are supported for example, by Example 4.

The amendments to claims 63, 71, 75, 81, 90, 94, and 102 are supported by the disclosure as filed. Use of an inducible promoter is supported by page 39, last paragraph, to page 40, first paragraph, as well as page 19, lines 3 to 11. "Low level expression" of less than 500 molecules of Gα15 protein per cell, for example, is supported for example on page 19, line 5 (claims 63, 71, 75, 81, 90, 94, and 102). An increase in expression of at least three-fold upon induction, is supported by page 19, line 7 (claims 63, 71, 75, 81, 90, 94, and 102). The recitation that the cell arises from a cell line subjected to functional cell analysis with a signal transduction detection system, is supported by the disclosure as filed, for example page 3, 2nd full paragraph and page 3, 3rd line from the bottom (claims 63, 71, 75, 81, 90, 94, and 102).

Applicants gratefully acknowledge the allowance of claim 1. Applicants also acknowledge withdrawal of previous rejections under 35 U.S.C. § 112, first paragraph, 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 103.

Specification

The title of the invention stands objected as allegedly not being descriptive. The title is amended herein as suggested in the Office Action. Applicants acknowledge with gratitude the Examiner's helpful suggestion. The objection to the title has been overcome. Therefore, Applicants respectfully request withdrawal of this objection.

The specification stands objected to because the priority information in the first paragraph of the specification allegedly indicates that the present application is a continuation-in-part of a provisional application. The first paragraph has been amended to recite that the present invention claims priority under U.S. Provisional patent application 60/020,234. Therefore, the objection to the specification has been overcome, and Applicants respectfully request withdrawal of the objection.

Claim Objections

The Office Action objects to numerous claims based on typographical or other obvious errors, as set out below. One of ordinary skill will recognize that amendments made herein related to the claim objections, are not intended to narrow the scope of the claims.

Claims 63, 81, 94 and 102, and claims depending therefrom, stand objected in allegedly missing the word "and" between the words "reporter gene," and "c) a third." The word "and" has been inserted at the indicated location in these claims. Therefore, this objection to the claims has been overcome, and Applicants respectfully request withdrawal of the objection.

Claims 71, 75, and 90, and claims depending therefrom, stand objected in allegedly being organized in an outline form that is different than other independent claims. Claims 71, 75, and 90 are amended herein to be identical in outline form, to other independent claims. Therefore, this objection to the claims has been overcome, and Applicants respectfully request withdrawal of the objection.

Claim 81, and claims depending therefrom, stand objected in that allegedly the syntax of claim 81 can be improved by putting the number "95" and the "%" on the same line. The claim amendments herein, remove the space between "95" and "%" in all the independent claims. Therefore, "95%" appears together on the same line for all independent claims, including claim 81. Accordingly, this objection to the claims has been overcome, and Applicants respectfully request withdrawal of the objection.

Claims 88 and 101 stand objected because they depend from a base claim, rather than from a claim which recites a method of increasing calcium levels in the cell, as is the case for claim 70. Claims 88 and 101 are amended herein to depend from a claim which recites a method of increasing calcium levels in the cell. Applicants gratefully acknowledge the Examiner's suggestion. Therefore, this objection to the claims has been overcome, and Applicants respectfully request withdrawal of the objection.

Claim 102 stands objected in that "steps of" is followed by a period instead of a colon. Claim 102 as amended includes a colon after "steps of." Therefore, this objection to the claims has been overcome, and Applicants respectfully request withdrawal of the objection.

Claim 107 stands objected in that "the cell" allegedly should be replaced with "said cells." Claim 107 as amended includes the term "cells" rather than "cell." Therefore, this objection to the claims has been overcome, and Applicants respectfully request withdrawal of the objection.

Claims 116 and 117 stand objected because there allegedly was no space between "claim" and "106." Amended claims 116 and 117 include a space between "claim" and "106." Therefore, this objection to the claims has been overcome, and Applicants respectfully request withdrawal of the objection.

Claim 137 stands objected because it was recommended to replace the word "detected" with ", wherein said change is detected." Amended claim 137 includes the phrase ", wherein said change is detected" in place of the last occurrence of "detected" in the claim. Therefore, this objection to the claims has been overcome, and Applicants respectfully request withdrawal of the objection.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 63, 66-71, 74, 75, 78-81, 84-90, 93, 94, 97-102, and 105-138 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of

identifying a GPCR for a given ligand, identifying a ligand for a given GPCR, or identifying modulators of GPCR signal transduction using only the stable cell lines produced in Example 4 of the specification, allegedly does not reasonably provide enablement for methods other than those using the stable cell line of Example 4. Applicants respectfully traverse the rejection.

The Office Action asserts that Applicants have shown that a stable cell line expressing promiscuous Gα15 protein can allegedly only be produced by co-transfecting COS-7 cells with (1) a gene encoding a Gα15 protein which is placed under the control of a CMV promoter operably linked to a heptamerized tet operator and (2) a tetracycline-dependent transactivator, rtTA that is also operably linked to a CMV promoter. The Office Action further alleges that since Applicants have argued through a Declaration under 37 CFR § 1.132 that the production of stable cell lines would not be obvious to a skilled artisan due to the requirement of essential steps not disclosed in the cited prior art, then it would not be predictable to one of ordinary skill in the art how to produce a stable cell line expressing promiscuous Gα15 protein other than by using the one specific method in the one specific cell line taught by the Applicants in Example 4 of the specification.

Applicants respectfully assert that the specification meets the 35 U.S.C. § 112, first paragraph enablement requirement with respect to claims 63, 66-71, 74, 75, 78-81, 84-90, 93, 94, 97-102, and 105-138. The Declaration of Dr. Mel Simon filed under 37 C.F.R. § 1.132 does *not* indicate that *only* cells of Example 4 can be used to practice the methods of the present invention. Rather, the Declaration indicates that " I and my co-inventors, created useful stable cell lines by functionally selecting them using ***a signal transduction detection system*** as described in the above referenced patent application" (Emphasis added). Furthermore, the Declaration indicates that prior art references do not teach one skilled in the art that stable expression of a G protein in a cell would be either excessive, causing toxicity or down-regulation, or insufficient for promiscuous coupling.

As amended, independent claims 63, 71, 75, 81, 90, 94, and 102, from which the remaining claims rejected under 35 U.S.C. § 112, first paragraph depend, recite the important considerations regarding the cell used in the methods of the invention, as indicated in the Declaration. These considerations include the following: that the cell of the method arises from a cell line subjected to functional cell analysis with a signal transduction detection system; and that the first heterologous promoter is inducible, providing an inducible expression of the Gα15 protein from a low level to a level that is sufficient to permit promiscuous coupling to the GPCR. Therefore, claims 63, 66-71, 74, 75, 78-81, 84-90, 93, 94, 97-102, and 105-138 are enabled by the disclosure as filed. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph. Furthermore, Applicants point out that newly added claims 139-145 recite that the cells are COS-7 cells wherein the first heterologous inducible promoter is a cytomegalovirus (CMV) promoter operably linked to a heptamerized tet operator, and wherein the cells further include a polynucleotide encoding a tetracycline-dependent transactivator operably linked to a constitutive promoter.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 63, 66-71, 74, 75, 78-81, 84-90, 93, 94, 97-102, and 105-138 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse the rejection.

Claims 63, 66-71, 74, 75, 78-81, 84-90, 93, 94, 97-102, and 105-138 stand rejected as being incomplete for allegedly omitting essential elements. The Office Action asserts that per the Applicants' Declaration under 37 CFR 1.132, the only way to produce a stable cell line which expresses promiscuous Gα15 protein is to co-transfect COS-7 cells with (1) a gene encoding a Gα15 protein which is placed under the control of a CMV promoter operably linked to a heptamerized tet operator and (2) a tetracycline-dependent transactivator, rtTA that is also

operably linked to a CMV promoter. Applicants respectfully disagree with this assertion in the Office Action.

Applicants respectfully assert that claims 63, 66-71, 74, 75, 78-81, 84-90, 93, 94, 97-102, and 105-138 meet the requirements of 35 U.S.C. § 112, second paragraph. The Declaration of Mel Simon filed under 37 C.F.R. § 1.132 does *not* indicate that the *only* way to produce cells to be used in methods of the present invention is by using the above-recited steps. Rather, the Declaration indicates that " I and my co-inventors, created useful stable cell lines by functionally selecting them using ***a signal transduction detection system*** as described in the above referenced patent application" (Emphasis added). Furthermore, the Declaration indicates that prior art references do not teach one skilled in the art that stable expression of a G protein in a cell would be either excessive, causing toxicity or down-regulation, or insufficient for promiscuous coupling.

As amended, independent claims 63, 71, 75, 81, 90, 94, and 102, from which the remaining claims rejected under 35 U.S.C. § 112, second paragraph depend, recite the important considerations regarding the cell used in the methods of the invention, as indicated in the Declaration. These considerations include the following: that the cell of the method arises from a cell line subjected to functional cell analysis with a signal transduction detection system; and that the first heterologous promoter is inducible, providing an increase in expression of the Gα15 protein from a low level to a level that is sufficient to permit promiscuous coupling to the GPCR. Therefore, claims 63, 66-71, 74, 75, 78-81, 84-90, 93, 94, 97-102, and 105-138 meet the requirements of 35 U.S.C. § 112, second paragraph.

Ciaims 75, 78-80, 122, 127, and 135 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being incomplete for omitting an essential step. The alleged omitted step is identifying the claimed ligand. Amended claim 75, from which claims 78-80, 122, 127, and 135 depend, recites that "a change in reporter gene expression identifies the test compound as a

ligand for the GPCR, thereby identifying the ligand for the GPCR." Therefore, claim 75 as amended meets the requirements of 35 U.S.C. § 112, second paragraph.

Claims 81, 84-89, 112, 113, 119, 123, 130, and 136 stand rejected under 35 U.S.C. § 112, second paragraph. The Office Action alleges that these claims are confusing since it is not understood what the "test chemical" encompasses and how it adds to the claim. Amended claim 81, from which claims 84-89, 112, 113, 119, 123, 130, and 136 depend, clarifies the relationship between the test chemical and the ligand. Amended claim 81 recites that a change in reporter gene expression after addition of the test chemical identifies the test compound as a ligand for the GPCR. Therefore, claims 81, 84-89, 112, 113, 119, 123, 130, and 136 meet the requirements of 35 U.S.C. § 112, second paragraph

Claims 90, 93, 94, 97-101, 114, 115, 120, 124, 125, 128, 131, 137, and 138 stand rejected under 35 U.S.C. § 112, second paragraph. The Office Action alleges that these claims are confusing in that the "test chemical" is added before the ligand. Amended claims 90 and 94 from which claims 93, 97-101, 114, 115, 120, 124, 125, 128, 131, 137, and 138 depend, clarify that the ligand is added before the test compound. Therefore, claims 90, 93, 94, 97-101, 114, 115, 120, 124, 125, 128, 131, 137, and 138 meet the requirements of 35 U.S.C. § 112, second paragraph.

Claims 118-121 stand rejected under 35 U.S.C. § 112, second paragraph. The Office Action alleges that these claims are confusing in that the reporter gene substrate is CCF2, a β-lactamase substrate, but the claims depend from claims in which the reporter gene is not limited to β-lactamase. Amended claims 118-121 depend from claims in which the reporter gene is recited to be β-lactamase, thereby clarifying that when the substrate is CCF2, the reporter gene encodes β-lactamase. Therefore, claims 118-121 meet the requirements of 35 U.S.C. § 112, second paragraph.

Claim 135 stands rejected under 35 U.S.C. § 112, second paragraph. The Office Action alleges that there is insufficient antecedent basis for "step (iii)." Amended claim 135 recites

"step (ii)" rather than "step (iii). Therefore, the typographical error has been corrected and claim 135 meets the requirements of 35 U.S.C. § 112, second paragraph.

Claims 133-137 stand rejected under 35 U.S.C. § 112, second paragraph. The Office Action alleges that these claims are confusing in reciting "second control cell" where there is no "first control cell." Amended claims 133-137 do not recite the word "second." Therefore, it is clarified that the claim refers to one control cell, and claims 133-137 meet the requirements of 35 U.S.C. § 112, second paragraph.

Claim 138 stands rejected under 35 U.S.C. § 112, second paragraph. The Office Action alleges that the claim is confusing in reciting that a control cell lacking the GPCR is detected under steps (i), (ii), and (iii), but step (i) recites that a cell is transfected with a polynucleotide encoding a GPCR. Amended claim 138 recites that the control cell is detected under the conditions of step (iii). Therefore, the typographical error has been corrected and claim 138 meets the requirements of 35 U.S.C. § 112, second paragraph.

Since all of the specific rejections under 35 U.S.C. § 112, second paragraph have been overcome, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: August 19, 2002

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Enclosure: Exhibit A

EXHIBIT A

MARKED VERSION OF CLAIMS SHOWING AMENDMENTS

In the Title:

Please amend the title as follows:

[PROMISCUOUS G-PROTEIN COMPOSITIONS AND THEIR USE] METHODS OF USING PROMISCUOUS G PROTEINS TO IDENTIFY G PROTEIN-COUPLED RECEPTORS AND THEIR LIGANDS.

In the Specification:

Please amend the first paragraph of the specification as follows:

This application claims priority under 35 U.S.C. Section 119 to provisional patent application 60/020,234 filed on June 21, 1996, by Negulescu et al., which is herein incorporated by reference [and of which this application is a continuation in part].

In the Claims

Please amend the claims as follows:

63. (Twice amended) A method of identifying a G-protein coupled receptor (GPCR) for a given ligand, the method comprising:

(i) providing a cell, said cell comprising,

a) a first heterologous inducible promoter operably linked to a first polynucleotide encoding a functional Gα15 protein having at least 95[ ]% sequence homology to SEQ. ID. NO. 2,

b) a second heterologous promoter operably linked to a second polynucleotide encoding a reporter gene, and

c) a third heterologous promoter operably linked to a third polynucleotide encoding said GPCR,

wherein said first heterologous inducible promoter provides for the low level expression prior to induction [said cell stably expresses said Gα15 protein],

wherein induction of said first heterologous inducible promoter provides for at least a three fold increase in expression of said Gα15 protein,

wherein induced expression of said Gα15 protein is sufficient [at levels] to permit promiscuous coupling to said GPCR,

wherein said GPCR is not naturally expressed in said cell, [and]

wherein said second heterologous promoter is directly or indirectly modulated by the activity of said Gα15 protein, and

wherein said cell arises from a cell line subjected to functional cell analysis with a signal transduction detection system;

(ii) contacting said cell with said ligand; and

(iii) detecting a change in reporter gene expression by comparing reporter gene expression prior to addition of said ligand with reporter gene expression after addition of said ligand.

71. (Three-times amended) A method for identifying a GPCR for a given ligand, the method comprising:

(i) providing a cell, said cell comprising,

a) a first heterologous inducible promoter operably linked to a first polynucleotide encoding a functional Gα15 protein having at least 95[ ]% sequence homology to SEQ. ID. NO. 2, and

b) a second heterologous promoter operably linked to a second polynucleotide encoding said GPCR,

wherein said first heterologous inducible promoter provides for the low level expression prior to induction, and [said cell stably expresses said Gα15 protein]

wherein induction of said first heterologous inducible promoter provides for at least a three fold increase in expression of said Gα15 protein, and

wherein induced expression of said Gα15 protein is [at] sufficient [levels] to permit promiscuous coupling to said GPCR,

[and] wherein said GPCR is normally coupled to either $G\alpha_i$, $G\alpha_s$ or $G\alpha_{12}$ in the absence of said Gα15 protein, [and]

wherein said GPCR is not naturally expressed in said cell, and

wherein said cell arises from a cell line subjected to functional cell analysis with a signal transduction detection system;

(ii) contacting said cell with said ligand; and

(iii) detecting a change in a signal with a signal transduction detection system by comparing said signal prior to addition of said ligand with said signal after addition of said ligand,

wherein said signal transduction detection system comprises a dye.

75. (Twice amended) A method of a identifying a ligand for a GPCR, the method comprising:

(i) contacting a cell with a test chemical, said cell comprising

a) a first heterologous inducible promoter operably linked to a first polynucleotide encoding a functional Gα15 protein having at least 95[ ]% sequence homology to SEQ. ID. NO. 2, and

b) a second heterologous promoter operably linked to a second polynucleotide encoding said GPCR,

wherein said first heterologous inducible promoter provides for the low level expression prior to induction, [said cell stably expresses said Gα15 protein]

wherein induction of said first heterologous inducible promoter provides for at least a three fold increase in expression of said Gα15 protein,

wherein induced expression of said Gα15 protein is [at] sufficient [levels] to permit promiscuous coupling to said GPCR, [and] wherein said GPCR is normally coupled to either $G\alpha_i$, $G\alpha_s$ or $G\alpha_{12}$ in the absence of said Gα15 protein, [and]

wherein said GPCR is not naturally expressed in said cell, and

wherein said cell arises from a cell line subjected to functional cell analysis with a signal transduction detection system; and

(ii) detecting a change in a signal with a signal transduction detection system by comparing said signal prior to addition of said test chemical with said signal after addition of said test chemical,

wherein said signal transduction detection system comprises a dye,

wherein a change in reporter gene expression identifies the test compound as a ligand for the GPCR, thereby identifying the ligand for the GPCR.

81. (Three-times amended) A method of identifying a ligand for a GPCR, the method comprising

(i) contacting a cell with a test chemical, said cell comprising,

a) a first heterologous inducible promoter operably linked to a first polynucleotide encoding a functional Gα15 protein having at least 95[ ]% sequence homology to SEQ. ID. NO. 2,

b) a second heterologous promoter operably linked to a second polynucleotide encoding a reporter gene, and

c) a third heterologous promoter operably linked to a third polynucleotide encoding said GPCR,

wherein said first heterologous inducible promoter provides for the low level expression prior to induction [said cell stably expresses said Gα15 protein], and

wherein induction of said first heterologous inducible promoter provides for at least a three fold increase in expression of said Gα15 protein, and

wherein induced expression of said Gα15 protein is sufficient [at levels] to permit promiscuous coupling to said GPCR,

wherein said GPCR is not naturally expressed in said cell, and

wherein said second heterologous promoter is directly or indirectly modulated by the activity of said Gα15 protein, and

wherein said cell arises from a cell line subjected to functional cell analysis with a signal transduction detection system; and

(ii) detecting a change in reporter gene expression by comparing reporter gene expression prior to addition of said [ligand] test chemical with reporter gene expression after addition of said [ligand] test chemical, wherein a change in reporter gene expression identifies the test compound as a ligand for the GPCR, thereby identifying the ligand for the GPCR.

88. (Amended) The method of claim [81] 86, further comprising contacting said cell with phorbol myristate acetate or an analog thereof.

90. (Three-times amended) A method for identifying a modulator of signal transduction mediated by GPCR activation in a cell, the method comprising:

[a)](i) contacting a cell with [a test chemical,] a ligand that in the absence of a test chemical, activates signal transduction in said cell, said cell comprising

a) a first heterologous inducible promoter operably linked to a first polynucleotide encoding a functional Gα15 protein having at least 95[ ]% sequence homology to SEQ. ID. NO. 2, and

b) a second heterologous promoter operably linked to a second polynucleotide encoding said GPCR,

wherein said first heterologous inducible promoter provides for the low level expression prior to induction, and [said cell stably expresses said Gα15 protein

wherein induction of said first heterologous inducible promoter provides for at least a three fold increase in expression of said Gα15 protein, and

wherein induced expression of said Gα15 protein is [at] sufficient [levels] to permit promiscuous coupling to said GPCR,

[and] wherein said GPCR is normally coupled to either $G\alpha_i$, $G\alpha_s$ or $G\alpha_{12}$ in the absence of said Gα15 protein, [and]

wherein said GPCR is not naturally expressed in said cell, and

wherein said cell arises from a cell line subjected to functional cell analysis with a signal transduction detection system;

[b)](ii) contacting said cell with [a ligand that, in the absence of the test chemical, activates signal transduction in said cell,] the test compound, and

[c)](iii)detecting a change in a signal with a signal transduction detection system by comparing said signal prior to addition of said test chemical with said signal after addition of said test chemical.

94. (Three-times amended) A method for identifying a modulator of signal transduction in a cell, the method comprising:

(i) contacting a cell with [a test chemical,] a ligand that in the absence of a test chemical, activates signal transduction via a GPCR in said cell, said cell comprising,

a) a first heterologous inducible promoter operably linked to a first polynucleotide encoding a functional Gα15 protein having at least 95[ ]% sequence homology to SEQ. ID. NO. 2,

b) a second heterologous promoter operably linked to a second polynucleotide encoding a reporter gene, and

c) a third heterologous promoter operably linked to a third polynucleotide encoding said GPCR,

wherein said first heterologous inducible promoter provides for the low level expression prior to induction [said cell stably expresses said Gα15 protein],

wherein induction of said first heterologous inducible promoter provides for at least a three fold increase in expression of said Gα15 protein,

wherein induced expression of said Gα15 protein is sufficient [at levels] to permit promiscuous coupling to said GPCR,

wherein said GPCR is not naturally expressed in said cell, [and]

wherein said second heterologous promoter is directly or indirectly modulated by the activity of said Gα15 protein, and

wherein said cell arises from a cell line subjected to functional cell analysis with a signal transduction detection system;

(ii) contacting said cell with [a ligand that, in the absence of said test chemical activates signal transduction via said GPCR in said cell] the test compound; and

(iii) detecting a change in reporter gene expression by comparing reporter gene expression prior to addition of said test chemical with reporter gene expression after addition of said test chemical.

101. (Amended) The method of claim [94] 99, further comprising contacting said cell with phorbol myristate acetate or an analog thereof.

102. (Amended) A method of functionally profiling a test chemical comprising the steps of[.]:

(i) contacting a panel of cells with a test chemical, said panel of cells comprising[,] a plurality of cell clones, each cell clone comprising

a) a first heterologous <u>inducible</u> promoter operably linked to a first polynucleotide encoding a functional Gα15 protein having at least 95[ ]% sequence homology to SEQ. ID. NO. 2,

b) a second heterologous promoter operably linked to a second polynucleotide encoding a reporter gene, <u>and</u>

c) a third heterologous promoter operably linked to a third polynucleotide encoding said GPCR,

wherein <u>said first heterologous inducible promoter provides for the low level expression prior to induction</u> [said cell stably expresses said Gα15 protein],

<u>wherein induction of said first heterologous inducible promoter provides for at least a three fold increase in expression of said Gα15 protein,</u>

<u>wherein induced expression of said Gα15 protein is</u> sufficient [at levels] to permit promiscuous coupling to said GPCR,

wherein said second heterologous promoter is directly or indirectly modulated by the activity of said Gα15 protein,

wherein said GPCR is not naturally expressed in said cell, [and]

<u>wherein said cell arises from a cell line subjected to functional cell analysis with a signal transduction detection system; and</u>

wherein each cell clone differs only with respect to said GPCR that is expressed;

(ii) contacting said cell clones with a test chemical;

(iii) detecting reporter gene expression from said cell clones; and

(iv) comparing reporter gene expression between said cell clones.

107. The method of claim 102, further comprising contacting said [cell] cells with a compound that increases calcium levels inside said [cell] cells.

111. (Twice amended) The method of claim [67] 110, wherein said reporter gene is β-lactamase.

113. (Twice amended) The method of claim [85] 112, wherein said reporter gene is β-lactamase.

115. (Twice amended) The method of claim [98] 114, wherein said reporter gene is β-lactamase.

116. (Twice amended) The method of claim 106, further comprising contacting said cell with a reporter gene substrate.

117. (Twice amended) The method of claim 106, wherein said reporter gene is β-lactamase.

118. (Twice amended) The method of claim [110] 111, wherein said reporter gene substrate is CCF2.

119. (Twice amended) The method of claim [112] 113, wherein said reporter gene substrate is CCF2.

120. (Twice amended) The method of claim [114] 115, wherein said reporter gene substrate is CCF2.

121. (Twice amended) The method of claim [116] 117, wherein said reporter gene substrate is CCF2.

133. (Amended) The method of claim 63, wherein said method further comprises comparing said change in reporter gene expression detected in step (iii) with a change in reporter gene expression detected in a [second] control cell line lacking said GPCR detected under the same conditions as in step (iii).

134. (Amended) The method of claim 71, wherein said method further comprises comparing said change in signal detected in step (iii) with a change in signal detected in a [second] control cell line lacking said GPCR detected under the same conditions as in step (iii).

135. (Amended) The method of claim 75, wherein said method further comprises comparing said change in signal detected in step [(iii)] (ii) with a change in signal detected in a [second] control cell line lacking said GPCR detected under the same conditions as in step [(iii)] (ii).

136. (Amended) The method of claim 81, wherein said method further comprises comparing said change in reporter gene expression detected in step (ii) with a change in reporter gene expression detected in a [second] control cell line lacking said GPCR detected under the same conditions as in step (ii).

137. (Amended) The method of claim 90, wherein said method further comprises comparing said change in reporter gene expression detected in step [(]c) with a change in signal

detected in a [second] control cell line lacking said GPCR [detected] wherein said change is detected under the same conditions as in steps [(]b) and [(]c).

138. (Amended) The method of claim 94, wherein said method further comprises comparing said change in reporter gene expression detected in step (iii) with a change in reporter gene expression detected in a [second] control cell line lacking said $GPCR_1$ detected under the same conditions as in [steps (i), (ii) and] step (iii).